IN THE SPECIFICATION

Please replace the title at the top of page 1 as follows:

~~**PROBE COMPOSITION AND METHOD**~~ METHOD FOR DISTINGUISHING DIFFERENT-SEQUENCE POLYNUCLEOTIDES.

Please replace the paragraph at page 1, lines 2 to 12 (the original paragraph at page 1, lines 2 to 12 was replaced with a replacement paragraph in the Preliminary Amendment filed April 14, 2004) with the following paragraph:

This application is a continuation of U.S. Patent Application No. 10/170,044, filed June 10, 2002, now U.S. Patent No. 6,756,204, which is a continuation application of U.S. Patent Application No. 09/580,103, filed May 30, 2000, which is a continuation application of U.S. Patent Application No. 09/152,354, filed September 14, 1998, abandoned, which is a continuation application of U.S. Patent Application No. 08/877,460, filed June 17, 1997 now U.S. Patent No. 5,807,682, which is a continuation application of U.S. Patent Application No. 08/561,478, filed November 21, 1995 now U.S. Patent No. 5,703,222, which is a continuation application of U.S. Patent Application No. 07/866,018, filed April 7, 1992 now U.S. Patent No. 5,470,705, which is a continuation-in-part application of U.S. Patent Application No. 07/862,642, filed April 3, 1992, abandoned, all of which are incorporated herein by reference.

Please replace the paragraph beginning on page 9, line 14, and ending on page 9, line 17, with the following paragraph:

Figures 10A-10C illustrate a method [[oof]] of detecting target sequences by ligation of base-matched probes by ligase chain reaction (LCR) in accordance with the first general embodiment of the invention;

Please replace the paragraph beginning on page 10, line 12, and ending page 10, line 14, with the following paragraph:

Figures 18A[[-18C]] and 18B illustrate an alternative probe-ligation method, in accordance with the first general embodiment of the invention;

Please replace the paragraph beginning on page 14, line 34, and ending on page 15, line 8, with the following paragraph:

Preferred polymer chains are those which are hydrophilic, or at least sufficiently hydrophilic when bound to the oligonucleotide binding polymer to ensure that the probe is readily soluble in aqueous medium. The polymer chain should also not effect the hybridization reaction. Where the binding polymers are highly charged, as in the case of oligonucleotides, the ~~binding polymers~~ polymer chains are preferably uncharged or have a charge/subunit density which is substantially less than that of the binding polymer.

Please replace the paragraphs beginning on page 20, line 22, and ending on page 21, line 2, with the following two paragraphs:

Figure 2[[A]] illustrates one method for preparing PEO chains having a selected number of HEO units. As shown in the figure, HEO is protected at one end with

dimethoxytrityl (DMT), and activated at its other end with methane sulfonate. The activated HEO can then react with a second DMT-protected HEO group to form a DMT-protected HEO dimer. This unit-addition is carried out successively until a desired PEO chain length is achieved. Details of the method are given in Example 1.

Example 2 describes the sequential coupling of HEO units through uncharged bisurethane tolyl groups. Briefly, with respect to Figure [[2B]] 3, HEO is reacted with 2 units of tolyene-2,4-diisocyanate under mild conditions, and the activated HEO is then coupled at both ends with HEO to form a bisurethane tolyl-linked trimer of HEO.

Please replace the paragraph beginning on page 28, line 1, and ending on page 28, line 10, with the following paragraph:

Example 7 illustrates the general principles of probe ligation and separation, in accordance with this aspect of the invention. In this method, a 25-base oligonucleotide derivatized with 1 or 2 Phe-Ala-Phe-Ala (SEQ ID NO: 4) tetrapeptide units and a fluorescent-labeled 25-base oligonucleotide were mixed under hybridization conditions with a target polynucleotide whose sequence spanned the two oligonucleotides. The hybridized probe elements were treated with ligase, to form fluorescent-labeled probes [[with]] carrying 1 or 2 tetrapeptide units.

Please replace the paragraph beginning on page 46, line 18, and ending on page 46, line 27, with the following paragraph:

A 48-base oligonucleotide having the sequence

5'GCACCATTAAAGAAAATATCATCTTTGGTGTTTCCTATGATGAATATA

carboxyfluorescein-3' (SEQ ID NO: 1) (composition 10 in Figure 4A) was prepared using a 3'-linked carboxyfluorescein polystyrene support (Applied Biosystems, Inc.) or can be prepared using 3'-Amine-ON (oligonucleotide) CPG (Clontech, Palo Alto, CA) and FAM-NHS (ABI) according to published methods (Applied Biosystems, Caruthers, Connell) and standard phosphoramidite chemistry on an Applied Biosystems 380B DNA Synthesizer.

Please replace the paragraph beginning on page 47, line 29, and ending on page 48, line 2, with the following paragraph:

A 26 base oligonucleotide having the sequence 5' TTG GTG TTT CCT ATG ATG AAT ATA-LAN-T3' (SEQ ID NO: 2) was made on an ABI model 380B DNA synthesizer using standard phosphoramidite chemistry (composition 15 in Figure 5). LAN is a base modified deoxyuridine phosphoramidite (Molecular Biosystems Inc.) with a TFA protected amine. The 26 mer was made from a 1 μm column using trityl on manual protocol after completion of synthesis. The column material was divided into 10 separate 0.1 μmol columns.

Please replace the paragraph beginning on page 48, line 32, and ending on page 49, line 2, with the following paragraph:

A 25 base oligonucleotide having the sequence 5' GGC ACC ATT AAA GAA AAT ATC ATC T 3' (SEQ ID NO: 3) was made as described in Example 4A. DMT-protected phosphoramidite HEO units were added to the 5' end of this 25 mer and purified as described in Example 4B.

Please replace the paragraph beginning on page 49, line 22 and ending on page 49, line 30, with the following paragraph:

The synthesis column was then placed onto an ABI DNA synthesizer and the peptide-oligonucleotide was cleaved off the support and purified by HPLC using the conditions as previously described to produce the peptide-oligonucleotides Ac (Phe-$Ala_{2\ or\ 4}$-$NH(CH_2)_6$-phosphate 5' GGC ACC ATT AAA GAA-AAT ATC ATC T-3' (SEQ ID NO: 3). Ligation of the peptide-oligonucleotide to a fluorescent-labeled oligonucleotide in the presence of an oligonucleotide target was performed as described in Example 7A. CE analysis is shown in Figure 9.

Please replace the paragraph beginning on page 50, line 33, and ending on page 51, line 7, with the following paragraph:

A first probe having the sequence 5' GGC ACC ATT AAA GAA AAT ATC ATC T-3' (SEQ ID NO: 3) was derivatized with [[a]] either a tetrapeptide Phe-Ala-Phe-Ala (SEQ ID NO: 4), or an octapeptide Phe-Ala-Phe-Ala-Phe-Ala-Phe-Ala (SEQ ID NO: 5) according to methods given in Example 5. A second probe having the sequence 5' P-TTG GTG TTT CCT ATG ATG AAT ATA G JOE 3' (SEQ ID NO: 6) was prepared by standard methods.

Please replace the paragraph beginning on page 52, line 10, and ending on page 52, line 24, with the following paragraph:

The following four probes were prepared:

(1) 5' GGC ACC ATT AAA GAA AAT ATC ATC T-3' (SEQ ID NO: 3) derivatized at its 5' end with [[a]] either a 2 or 4 unit DEO (dodecyl ethylene oxide) polymer chains, according to synthetic methods described in Example 4, except in this case the units are 12mers (2 or 4 12mers) of ethylene oxide;

(2) 5' P-TTG GTG TTT CCT ATG ATG AAT ATA G 3'-JOE (SEQ ID NO: 6), prepared as in Example 7.

(3) 5' ROX-CTA TAT TCA TCA TAG GAA ACA CCA AA 3'-OH (SEQ ID NO: 7), prepared according to published methods (Applied Biosystems); and

(4) 5'-P-GAT GAT ATT TTC TTT AAT GGT GCC-3' TAMRA (SEQ ID NO: 8), prepared with 3'-Amine-ON CPG, 5'-Phosphate-ON and Tamra-NH5 (ABI) using published methods (Applied Biosystems, Caruthers, Connell).

Please insert the enclosed sequence listing starting on a new page immediately following the abstract on page 61.